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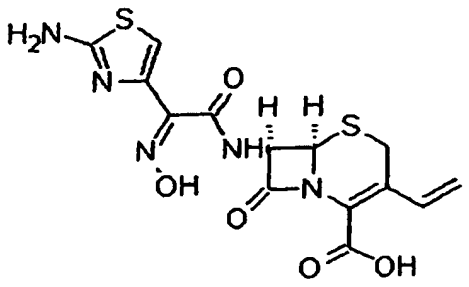
(54) Title: CRYSTALLINE FORMS OF CEFDINIR



(I)

(57) Abstract: The invention relates to processes for the preparation of crystalline polymorphic forms of cefdinir of formula (I). More particularly, it relates to the preparation of crystalline polymorphic forms of cefdinir designated as Forms B and C. The invention also relates to pharmaceutical compositions that include the polymorphic forms B and C, and the use of the compositions for treating bacterial infections.

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Description

CRYSTALLINE FORMS OF CEFDINIR

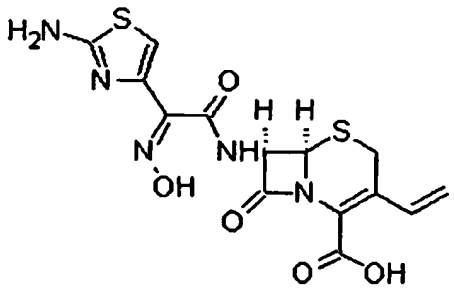
[1] Field of the Invention

[2] The field of the invention relates to processes for the preparation of crystalline polymorphic forms of cefdinir. More particularly, it relates to the preparation of crystalline polymorphic forms of cefdinir designated as Forms B and C. The invention also relates to pharmaceutical compositions that include the polymorphic Forms B and C, and the use of the compositions for treating bacterial infections.

[3] Background of the Invention

[4] Chemically, cefdinir is [(-)6R,7R] - 7-((Z)-2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido)-3-vinyl-8-oxo-5-thia-1-aza bicyclo[4.2.0]oct-2-ene-2-carboxylic acid having the structural Formula I. It is a third-generation semi-synthetic cephalosporin for oral use, characterized by broad antibacterial spectrum against gram-positive and gram-negative bacteria. In particular, the cefdinir shows excellent antibacterial activity against *Streptococci* and *Staphylococci*.

[5]



[6] **FORMULA I**

[7] U.S. Patent No. 4,559,334 discloses a process for the preparation of cefdinir in amorphous form by lyophilization. The amorphous form so produced is highly hygroscopic and therefore very difficult to formulate.

[8] U.S. Patent No. 4,935,507 discloses a crystalline Form A of cefdinir having a specific X-Ray diffraction pattern as shown in Figure 1.

[9] U.S. Application No. 20030204082 discloses a crystalline form of cefdinir (hereinafter designated as Form R) having a specific X-Ray diffraction pattern as shown in Figure 2.

[10] U.S. Application No. 20040242556 discloses a crystalline form of cefdinir designated as Form B having a specific X-Ray diffraction pattern. Form B is prepared from crystalline Form A by first forming a trifluoroacetic acid salt followed by basification with ammonia.

[11] U.S. Patent No. 6,350,869 describes a process for the preparation of the crystalline dicyclohexylamine salt of cefdinir and monohydrate form of cefdinir.

[12] International (PCT) Publication No. WO 04/46154 describes the amorphous monohydrate of cefdinir and a process for preparation thereof.

[13] Several processes have been reported for the preparation of crystalline salts of cefdinir which are either useful as intermediates in preparation of cefdinir or can be used as broad spectrum antimicrobials, for example, in International (PCT) Publication Nos. WO 02/98884; 04/16623; and 04/56835.

[14] International (PCT) Publication No. WO 03/50124 describes crystalline cefdinir potassium monohydrate and process for preparation thereof. The application further details utilization of the potassium salt of cefdinir in monohydrate form as potential antimicrobial agent.

[15] The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description, figures, and claims.

[16] Description of the Drawings

[17] Figure 1 is an X-ray powder diffraction pattern of Form A of cefdinir.

[18] Figure 2 is an X-ray powder diffraction pattern of crystalline cefdinir obtained as per U.S. Application No. 20030204082.

[19] Figure 3 is an X-ray powder diffraction pattern of crystalline Form B of cefdinir.

[20] Figure 4 is a differential scanning calorimetrythermogram of crystalline Form B of cefdinir.

[21] Figure 5 is an infrared spectrum of crystalline Form B of cefdinir.

[22] Figure 6 is an X-ray powder diffraction pattern of Form C of cefdinir.

[23] Figure 7 is a differential scanning calorimetrythermogram of polymorphic Form C of cefdinir.

[24] Figure 8 is an infrared spectrum of crystalline Form C of cefdinir.

[25] Summary of the invention

[26] In one general aspect there is provided a crystalline Form B of cefdinir.

[27] The Form B of cefdinir may have the X-ray diffraction pattern of Figure 3, differential scanning calorimetry thermogram of Figure 4, and infrared spectrum of Figure 5.

[28] In another general aspect there is provided a pharmaceutical composition that includes a therapeutically effective amount of the crystalline Form B of cefdinir; and one or more pharmaceutically acceptable carriers, excipients or diluents.

[29] In one general aspect there is provided a crystalline Form C of cefdinir.

[30] The Form C of cefdinir may have the X-ray diffraction pattern of Figure 6, differential scanning calorimetrythermogram of Figure 7, and infrared spectrum of Figure

8.

[31] In another general aspect there is provided a pharmaceutical composition that includes a therapeutically effective amount of the crystalline Form C of cefdinir; and one or more pharmaceutically acceptable carriers, excipients or diluents.

[32] In another general aspect there is provided a process for the preparation of crystalline form of cefdinir. The process includes converting cefdinir or a base addition salt thereof to cefdinir acid addition salt with an acid at a temperature of about 10°C or less; basifying the acid addition salt with a base; and isolating crystalline cefdinir.

[33] The process may include further drying of the product obtained.

[34] The process may produce Form B or Form C of crystalline cefdinir. It may produce the hydrated form of crystalline cefdinir.

[35] In another general aspect there is provided a pharmaceutical composition that includes a therapeutically effective amount of one or both of the crystalline Form B and the crystalline Form C of cefdinir, and one or more pharmaceutically acceptable carriers, excipients or diluents.

[36] Embodiments of the pharmaceutical compositions may include one or more of the following features or those described above. For example, the cefdinir may be either substantially pure crystalline Form B cefdinir or substantially pure crystalline Form C cefdinir.

[37] In another general aspect there is provided a method of treating bacterial infections in a warm-blooded animal. The method includes providing a pharmaceutical composition to the warm-blooded animal, the pharmaceutical composition comprising one or both of the crystalline Form B and the crystalline Form C of cefdinir.

[38] Embodiments of the method may include one or more of the following features or those described above. For example, the cefdinir may be either substantially pure crystalline Form B cefdinir or substantially pure crystalline Form C cefdinir.

[39] Detailed Description of the Invention

[40] The inventors have developed a novel process for preparation of crystalline polymorphic forms of cefdinir. The present inventors also have surprisingly found new polymorphic forms of cefdinir, which are characteristically different from the existing crystalline forms of cefdinir. The new polymorphic forms are designated as Forms B and C of cefdinir. All these forms are found to be stable under normal and accelerated storage conditions.

[41] Hereinafter the term 'crystalline cefdinir' refers to any crystalline polymorphic form of cefdinir. The term 'Form B' of cefdinir refers to crystalline cefdinir having X-Ray Powdered Diffraction (XRPD) pattern as depicted in Figure 3. The term 'Form C' of cefdinir refers to crystalline cefdinir having X-Ray Powdered Diffraction (XRPD) pattern as depicted in Figure 5.

[42] A first aspect of the present invention provides a process for the preparation of crystalline cefdinir wherein the process includes the steps of:

[43] (a) converting cefdinir to cefdinir acid addition salt at a temperature of 10°C or less;

[44] (b) optionally isolating the acid addition salt obtained in step a);

[45] (c) basifying the acid addition salt of cefdinir with a base; and

[46] (d) isolating crystalline cefdinir from the reaction mixture thereof.

[47] Cefdinir is suspended in an organic solvent or water at a temperature of 10°C or less. The resultant mixture is acidified with a suitable acid. The resultant mass is stirred and the precipitated solids are filtered, washed with water. The product obtained is dried to yield cefdinir acid addition salt.

[48] The organic solvent can be selected from one or more of esters, lower alkanols, ethers, ketones, polar aprotic solvents, halogenated hydrocarbons or mixtures thereof.

[49] The acid used is one or more inorganic or organic acids selected from one or more of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, trifluoroacetic acid (TFA), p-toluenesulphonic acid (pTSA), maleic acid, acetic acid, succinic acid and the like.

[50] The acid addition salt is basified with a base to a pH of about 1 to about 3, stirred and the precipitated solids are filtered, washed with water. The product obtained is dried to yield crystalline cefdinir. Forms B and C of cefdinir can be easily prepared by following the processes of the present invention.

[51] The base used can be selected from one or more inorganic or organic bases such as alkali and alkaline earth metal hydroxide or alkoxide, ammonia, triethylamine, dicyclohexylamine amine or diisopropylamine and the like.

[52] A second aspect of the present invention provides a process for the preparation of crystalline cefdinir wherein the process includes the steps of:

[53] (a) converting a base addition salt of cefdinir to cefdinir acid addition salt;

[54] (b) optionally isolating the acid addition salt of cefdinir,

[55] (c) basifying the acid addition salt of cefdinir with a base; and

[56] (d) isolating crystalline cefdinir from the reaction mixture thereof.

[57] Base addition salt of cefdinir is a salt of cefdinir with inorganic or organic base. Several such base addition salts are known to skilled artisans. The base addition salt of cefdinir is suspended in an organic solvent and acidified using a suitable acid to adjust the pH of this mixture to between about 1 to about 3. The resultant mass is stirred and the mixture is suitably worked up to provide an acid addition salt of cefdinir. The acid addition salt is then converted to crystalline form of cefdinir by basification as described in the first aspect of the invention.

[58] The organic solvent optionally contains water and can be selected from one or more of esters, lower alkanols, ethers, ketones, polar aprotic solvents, halogenated hy-

drocarbons or mixtures thereof.

[59] The suitable acid, which is used for preparation of the acid addition salt, and the base, which is used for basifying the acid addition salt, have already been described above.

[60] A third aspect of the present invention provides a process for the preparation of crystalline cefdinir wherein the process includes the steps of:

[61] (a) acidifying an isolated base addition salt of cefdinir at a temperature of 10°C or less; and

[62] (b) isolating crystalline cefdinir from the reaction mixture thereof.

[63] A suspension or solution of an isolated base addition salt of cefdinir is acidified using a suitable acid described earlier at a temperature of less than 10°C. The separated crystalline product is filtered, washed with water and dried to get crystalline cefdinir.

[64] Forms B and C of cefdinir can be easily prepared by following the processes described in the first, second or third aspects of the present invention.

[65] A fourth aspect of the present invention relates to a process for preparation of crystalline Form B of cefdinir wherein the process includes the steps of:

[66] (a) dissolving cefdinir or salt thereof in water at pH of about 5.5 to 8;

[67] (b) optionally adding an organic solvent in the solution of step a);

[68] (c) adjusting the pH of solution obtained in step a) or b) between 1.0 and 3.0 with an acid; and

[69] (d) isolating crystalline Form B of cefdinir from the reaction mixture obtained thereof.

[70] Cefdinir or salt thereof to be used as a starting material can be prepared by conventional methods reported in the literature, including U.S. Patent Nos. 4,559,334; 4,935,507; 4,870,168; 6,350,869 and 6,093,814; PCT Patent Application Nos. WO 98/45299; WO 99/55710; WO 02/98884; WO 03/91261; WO 04/16623; WO 04/35800; WO 04/56835; WO 04/58695 and WO 04/46154.

[71] Cefdinir or salt thereof is first suspended in water and the resultant mixture is cooled to about - 20 to 25°C. Preferably the temperature is adjusted in the range of -10 to 20°C. To this mixture a suitable base is added in order to adjust the pH of the reaction mass in the range of 5.5 to 8. The bases are common bases known to persons of ordinary skills in the art and include one or more of alkali or alkaline earth metal hydroxide, alkali or alkaline earth metal carbonate, alkali or alkaline earth metal bi-carbonate, alkali or alkaline earth metal alkoxide, alkali or alkaline earth metal hydride or an amine. The amine can be a primary, secondary or tertiary amine having alkyl, aryl, aralkyl, cycalkyl or heterocycle as substituent groups.

[72] A clear solution thus obtained can be further diluted with a suitable organic solvent selected from one or more of water soluble alkanols, ketones, esters, acetonitrile,

tetrahydrofuran, 1,4-dioxane, N,N-dimethylacetamide, N,N-dimethylformamide, N-methylpyrrolidone and dimethylsulphoxide or mixtures thereof.

[73] The pH of the clear solution is then adjusted using an acid in the range of 1.0 to 3.0. The acid can be a mineral acid or an organic acid such as carboxylic or sulphonic acid.

[74] The resultant mass is stirred at 0 to 30°C for 5 to 30 hours and the precipitated solids are filtered and washed with water. The product obtained is dried at room temperature to yield crystalline Form B of cefdinir.

[75] A fifth aspect of the present invention relates to a process for preparation of polymorphic Form C of cefdinir in which the process includes the steps of:

[76] (a) dissolving cefdinir or salt thereof in water at pH of about 5.5 to 8;

[77] (b) optionally adding an organic solvent in the solution of step a);

[78] (c) adjusting the pH of solution obtained in step a) or b) to between 1.0 and 3.5 with an acid; and

[79] (d) isolating the polymorphic Form C of cefdinir from the reaction mixture obtained thereof.

[80] Cefdinir or salt thereof to be used as starting material can be prepared by conventional methods reported in the literature, such as in U.S. Patent Nos. 4,559,33; 4,935,507; 4,870,168; 6,350,869 and 6,093,814; PCT Patent Application Nos. WO 98/45299; WO 99/55710; WO 02/98884; WO 03/91261; WO 04/16623; WO 04/35800; WO 04/56835; WO 04/58695 and WO 04/46154.

[81] Cefdinir or salt thereof is first suspended in water and the resultant mixture is cooled to about - 20 to 25°C. Preferably the temperature is adjusted in the range of -10 to 20°C. To this mixture a suitable base is added in order to adjust the pH of the reaction mass in the range of 5.5 to 8. The bases are common bases known to persons of ordinary skills in the art and include one or more of alkali or alkaline earth metal hydroxide, alkali or alkaline earth metal carbonate, alkali or alkaline earth metal bi-carbonate, alkali or alkaline earth metal alkoxide, alkali or alkaline earth metal hydride or ammonia or an amine. The amine can be primary, secondary or tertiary amine having alkyl, aryl, aralkyl, cycalkyl or heterocycle as substituent groups.

[82] The clear solution thus obtained can be decolorized using charcoal and further diluted with a suitable organic including one or more solvent selected from alkanols, esters, ketones, acetonitrile, chlorinated hydrocarbons, tetrahydrofuran, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, 1,4-dioxane and dimethylsulphoxide or mixtures thereof.

[83] The pH of the clear solution is then adjusted using an acid in the range of 1.0 to 3.5. The acid can be mineral acid or an organic acid such as carboxylic or sulphonic acid.

[84] The resultant mass is stirred at 0 to 25°C for sufficient time to precipitate Form C of cefdinir. The separated solids are filtered and washed with water. The product obtained

is dried at room temperature to yield crystalline Form C of cefdinir.

[85] A sixth aspect of the present invention provides crystalline Form B of cefdinir. A seventh aspect of the present invention provides crystalline Form B of cefdinir having a characteristic XRD pattern as depicted in Figure 3.

[86] An eighth aspect of the present invention provides crystalline Form B of cefdinir having characteristic absorption bands at two-theta values of 8.34 ± 0.2, 10.56 ± 0.2, 11.8 ± 0.2, 14.04 ± 0.2, 15.04 ± 0.2, 17.92 ± 0.2, 18.54 ± 0.2, 18.90 ± 0.2, 20.52 ± 0.2, 21.06 ± 0.2, 21.22 ± 0.2, 22.08 ± 0.2, 23.62 ± 0.2, 25.08 ± 0.2, 25.72 ± 0.2, 26.16 ± 0.2, 27.44 ± 0.2, 28.24 ± 0.2, 28.50 ± 0.2, 30.42 ± 0.2, 32.00 ± 0.2, 35.84 ± 0.2 and 38.82 ± 0.2.

[87] A ninth aspect of the present invention provides crystalline cefdinir having characteristic DSC melting exotherms obtained at about 78-85°C and about 160-170°C. The DSC thermogram of cefdinir is provided as Figure 4.

[88] A tenth aspect of the present invention provides crystalline Form B of cefdinir having a characteristic Fourier Transform Infrared (FTIR) spectrum as depicted in Figure 5.

[89] An eleventh aspect of the present invention provides crystalline cefdinir having a moisture content of about 12 to 14% w/w as measured by Thermal Gravimetric Analysis (TGA) and Karl Fischer analysis.

[90] A twelfth aspect of the present invention provides the crystalline Form C of cefdinir. A thirteenth aspect of the present invention provides crystalline Form C of cefdinir having a characteristic XRD pattern as depicted in Figure 6.

[91] A fourteenth aspect of the present invention provides crystalline Form C of cefdinir having characteristic absorption bands at two-theta values of 9.12 ± 0.2, 10.72 ± 0.2, 15.04 ± 0.2, 17.96 ± 0.2, 18.66 ± 0.2, 20.92 ± 0.2, 21.44 ± 0.2, 22.32 ± 0.2, 23.66 ± 0.2, 24.18 ± 0.2, 25.72 ± 0.2, 26.26 ± 0.2, 27.48 ± 0.2, 28.30 ± 0.2, 30.42 ± 0.2, 32.06 ± 0.2, 35.76 ± 0.2, 38.80 ± 0.2 and 39.22 ± 0.2.

[92] A fifteenth aspect provides crystalline Form C of cefdinir having a differential scanning calorimetric (DSC) thermogram as depicted in Figure 7.

[93] A sixteenth aspect of the present invention provides crystalline cefdinir having a characteristic melting exotherm obtained at about 120-130°C.

[94] A seventeenth aspect of the present invention provides crystalline Form C of cefdinir having characteristic Fourier Transform Infrared (FTIR) spectrum as depicted in Figure 8.

[95] An eighteenth aspect of the present invention provides a pharmaceutical composition comprising crystalline Form B or C of cefdinir along with pharmaceutically acceptable carrier(s) and/or excipient(s). The pharmaceutical compositions include one or more oral dosage forms such as tablets, capsules, liquid orals,

suspensions and the like, as well as topical dosage forms such as creams, lotions, ointments and the like.

[96] A nineteenth aspect of the present invention provides a method of treating bacterial infections comprising administering to a mammal in need thereof a therapeutically effective amount of crystalline Form B or C of cefdinir.

[97] Powder XRD of the samples were determined by using X-Ray Diffractometer, Rigaku Corporation, RU-H3R, Goniometer CN2155A3, X-Ray tube with Cu target anode, Divergence slits 1 0, Receiving slit 0.15mm, Scatter slit 1 , Power: 40 KV, 100 mA, Scanning speed: 2 deg/min step: 0.02 deg, Wave length: 1.5406 A

[98] FT-IR of the samples were determined by using a Perkin Elmer instrument,16 PC, SCAN: 16 scans, 4.0 cm-1, according to the USP 25, general test methods page 1920, infrared absorption spectrum by potassium bromide pellet method.

[99] DSC thermograms were recorded using DSC821 e, Mettler Toledo, Sample weight: 3-5 mg, Temperature range: 50-350°C, Heating rate: 10°C/min, Nitrogen 80.0 mL/min, Number of holes in the crucible: 1.

[100] While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

[101] Example 1: Preparation of crystalline Form B of cefdinir

[102] Cefdinir potassium salt (10 g) was suspended in de-mineralized water (300 ml) and cooled to 0-5°C. Methanol (60 ml) was added to this mixture followed by cooling again to 0-5°C. Dilute hydrochloric acid cooled to 0-5°C was added in one lot till pH of the solution was 2.2-2.3. The reaction mixture was stirred for 5 hours at 12-14°C. The separated solids were filtered, washed with de-mineralized water and dried to obtain the title compound. The yield was eight grams. The moisture contents was 13.69% w/w.

[103] Example 2: Preparation of cefdinir hydrochloride

[104] Cefdinir (80 g) was suspended in a mixture of denatured spirit (80 ml) and ethyl acetate (160 ml) at 0-5°C. Concentrated hydrochloric acid (17 ml) was added drop wise at 0-5°C to this mixture to get a clear solution. This clear acidified solution was added drop wise to ethyl acetate (3200 ml) at 0-5°C and the resultant mass was stirred vigorously for 1-2 hours. The precipitated solid was filtered, washed with ethyl acetate (500 ml), and dried to give the title compound. The yield was 96 grams.

[105] Example 3: Preparation of crystalline Form C of cefdinir

[106] Cefdinir hydrochloride (12 g) was dissolved in a mixture of tetrahydrofuran (30 ml) and water (150 ml). The solution was cooled to 18°C followed by addition of dichloromethane (10 ml). Dilute ammonia solution was added drop wise to the resultant mixture at 18-20°C till pH of 2.2 was reached. The reaction mixture was

stirred for 5 hours and the separated solid was filtered, washed with de-mineralized water (30 ml x 3) and dried to obtain the title compound. The yield was 9.2 grams. The moisture content was 12-14% w/w.

[107] Example 4: Preparation of cefdinir hydrochloride

[108] Cefdinir potassium salt (5 g) was suspended in de-mineralized water (25 ml). Concentrated hydrochloric acid (3.5 ml) was added to this mixture slowly till pH of about 1 was reached. Tetrahydrofuran (50 ml) was added to this acidified mixture and stirred for 5 minutes. Sodium chloride (10 g) was added to the reaction mixture followed by stirring. The organic layer was separated and tetrahydrofuran was recovered to yield an oily mass. Ethyl acetate (10 ml) and denatured spirit (5 ml) were added to the oily mass. The resultant mixture was cooled to 0-5°C. To this cooled mixture, concentrated hydrochloric acid (0.85 ml) was slowly added t o get a clear solution. This clear acidified solution was added to ethyl acetate (160 ml) at 0-5°C followed by stirring for 1 hour. The separated solid was filtered and dried to obtain the title compound. The yield was 3.5 grams.

[109] Example 5: Preparation of cefdinirpara-toluenesulphonic acid salt

[110] Cefdinir (20 g) was suspended in tetrahydrofuran (50 ml) and ethyl acetate (40 ml) at 0-5°C. To this mixture, para-toluenesulphonic acid was added (10.6 g) followed by stirring for 15-20 min to get a clear solution. This clear acidified solution was added drop-wise to previously cooled (0-5°C) ethyl acetate (1 L). The reaction mass was stirred for 1-2 hours at 0-5°C, filtered, and washed with ethyl acetate (100 ml). The separated solid was dried to obtain the title compound. The yield was twenty eight grams.

[111] Example 6: Preparation of crystalline Form C of cefdinir

[112] Cefdinir para-toluene sulphonic acid salt (12 g) was dissolved in a mixture of tetrahydrofuran (30 ml) and water (150 ml) and cooled to 18°C. To this solution, dichloromethane (10 ml) was added. Dilute ammonia was added drop-wise to the resultant mixture till a pH of 2.2 was reached. The reaction mixture was stirred for 5 hrs at 18°C. The separated solid was filtered, washed with de-mineralized water (30 ml x 3), and dried to obtain the title compound. The yield was 9.2 grams and the moisture content was 12-14%.

[113] Example 7: Preparation of cefdinirtrifluoroacetic acid salt

[114] Cefdinir (5 g) was suspended in de-mineralized water (200 ml) at room temperature. Trifluoroacetic acid (15 ml) was added drop-wise to this mixture to get a clear solution. This clear acidified solution was stirred for 0.5 hour. The separated solid was filtered, washed with cold water and dried to obtain the title compound. The yield was 4.8 grams.

[115] Example 8: Preparation of crystalline Form C of cefdinir

[116] Cefdinir trifluoroacetic acid salt (12 g) was dissolved in a mixture of tetrahydrofuran (30 ml) and water (150 ml) and cooled to 18°C. Dichloromethane (10 ml) was added to this solution. Dilute ammonia was added drop-wise to the resultant mixture till a pH of 2.2 was reached. The reaction mixture was stirred for 5 hrs at 18°C. The separated solid was filtered, washed with de-mineralized water (30 ml x 3) and dried to obtain the title compound. The yield was 9.2 grams and the moisture content was 12-14%.

[117] Example 9: Preparation of cefdinir hydrochloride

[118] Cefdinir potassium salt (20 g) was suspended in de-mineralized water (100 ml) at room temperature. Denatured spirit (30 ml) and ethyl acetate (100 ml) were added to this mixture. The resultant mixture was cooled to 0-4°C. To the cooled mixture, sodium chloride (32 g) was added followed by stirring for 2-3 minutes. Concentrated hydrochloric acid (8.8 ml, 2.2 M) was added drop wise to the resultant mixture. The organic layer was separated from this acidified mixture. The aqueous layer was washed again with a mixture of denatured spirit (15 ml) and ethyl acetate (50 ml) and the washings added to the previously separated organic layer. The combined organic layers were mixed and concentrated to about half the volume at 0-5°C. The resulting mass was added drop-wise to previously cooled (0-4°C) ethyl acetate (800 ml). The resultant mixture was stirred at 0-4°C for 1-1.5 hours and then filtered, washed with ethyl acetate (50 ml x 2) and dried to obtain the title compound. The yield was nineteen grams.

[119] Example 10: Preparation of crystalline Form C of cefdinir

[120] Cefdinir hydrochloride (18 g) was dissolved in a mixture of tetrahydrofuran (45 ml) and de-mineralized water (75 ml). This solution was stirred at room temperature and de-mineralized water (165 ml) was added followed by stirring at 18-19°C. Dilute ammonia solution was added drop-wise at 18-20°C to this mixture till a pH of 2.2-2.3 was reached. This reaction mixture was stirred for 5 hours at 18-19°C, filtered, washed with water (45 ml x 3) and dried to obtain the title compound. The yield was 11.5 grams and the moisture content was 12.84%.

[121] Example 11: Preparation of crystalline Form B of cefdinir

[122] Cefdinir potassium salt (10 g) was suspended in water (300 ml) and methanol (60 ml). This mixture was cooled to 0-4°C. To this cooled mixture, dilute hydrochloric acid pre-cooled to 5°C was added till pH of 2.2 was reached at 0-4°C. The reaction mixture was stirred for 5-6 hours at 12-14°C, filtered, washed with de-mineralized water (30 ml x 3) and dried to obtain the title compound. The yield was 8.9 grams and the moisture content was 13.7%.

[123] Example 12: Preparation of cefdinir hydrochloride

[124] Crystalline form B cefdinir (7.5 g) was suspended in a mixture of denatured spirit

(4.5 ml) and ethyl acetate (15 ml) at room temperature. This mixture was cooled to 0-5°C and concentrated hydrochloric acid (1.7 ml) was added drop wise at 0-5°C to get a clear solution. This clear acidified solution was added to pre-cooled ethyl acetate (300 ml) at 0-5°C. The resultant mixture was stirred for 1 hour, filtered, washed with ethyl acetate (20 ml x 3) and dried to obtain the title compound. The yield was 6.75 grams.

[125] Example 13: Preparation of crystalline Form B of cefdinir

[126] A stirred suspension of cefdinir (5 g) in water was cooled to about 0°C. The solid was dissolved by adjusting the pH of the mixture to about 5.5 to 8.0. Methanol was added to the clear solution followed by addition of dilute hydrochloric acid and water to adjust the pH at about 1.0 to 2.8 while maintaining the temperature of the reaction mass between 5 to 20°C. The resultant mass was stirred for about 12 to 14 hours and the precipitated solids were filtered and washed. The product was dried at room temperature to yield the crystalline Form B of cefdinir. The yield was 4.9 grams and the moisture content was 12% w/w.

[127] Example 14: Preparation of crystalline Form C of cefdinir

[128] A stirred suspension of cefdinir (5 g) in water was dissolved by adjusting the pH of the mixture to about 5.5 to 8.0. The clear solution was decolorized using activated charcoal (0.5 gm) and the resultant mixture was filtered. A mixture of tetrahydrofuran and dichloromethane (10 to 40 ml) was added to the clear filtrate. The solution so obtained was stirred at 5 to 20°C followed by addition of dilute hydrochloric acid to adjust the pH at about 2.0 to 3.0 while maintaining the temperature of the reaction mass between 5 to 20°C. The resultant mass was stirred for sufficient time to precipitate solids and the precipitated solids were filtered and washed. The product was dried at 40°C to yield the crystalline Form C of cefdinir. The yield was 4.79 grams and the moisture content was 12.0% w/w.

[129] While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention. For example, it is understood that the various polymorphic forms of cefdinir can be incorporated in dosage forms for treating conditions for which cefdinir is useful.

Claims

[1] Crystalline Form B of cefdinir having the X-ray diffraction pattern of Figure 3.

[2] The crystalline Form B of cefdinir of claim 1 having characteristic X-ray diffraction peaks at two-theta values of 8.34 ± 0.2, 10.56 ± 0.2, 11.8 ± 0.2, 14.04 ± 0.2, 15.04 ± 0.2, 17.92 ± 0.2, 18.54 ± 0.2, 18.90 ± 0.2, 20.52 ± 0.2, 21.06 ± 0.2, 21.22 ± 0.2, 22.08 ± 0.2, 23.62 ± 0.2, 25.08 ± 0.2, 25.72 ± 0.2, 26.16 ± 0.2, 27.44 ± 0.2, 28.24 ± 0.2, 28.50 ± 0.2, 30.42 ± 0.2, 32.00 ± 0.2, 35.84 ± 0.2 and 38.82 ± 0.2.

[3] The crystalline Form B of cefdinir of claim 1 having the differential scanning calorimetrythermogram of Figure 4.

[4] The crystalline Form B of cefdinir of claim 1 having characteristic differential scanning calorimetric melting exotherms at about 78-85°C and about 160-170°C.

[5] The crystalline Form B of cefdinir of claim 1 having the infrared spectrum of Figure 5.

[6] Crystalline cefdinir having a moisture content of about 12 to 14% w/w as measured by Thermal Gravimetric Analysis and Karl Fischer analysis.

[7] Crystalline Form C of cefdinir having the X-ray diffraction pattern of Figure 6.

[8] The crystalline Form C of cefdinir of claim 7 having characteristic X-ray diffraction peaks at two-theta values of 9.12 ± 0.2, 10.72 ± 0.2, 15.04 ± 0.2, 17.96 ± 0.2, 18.66 ± 0.2, 20.92 ± 0.2, 21.44 ± 0.2, 22.32 ± 0.2, 23.66 ± 0.2, 24.18 ± 0.2, 25.72 ± 0.2, 26.26 ± 0.2, 27.48 ± 0.2, 28.30 ± 0.2, 30.42 ± 0.2, 32.06 ± 0.2, 35.76 ± 0.2, 38.80 ± 0.2 and 39.22 ± 0.2.

[9] The crystalline Form C of cefdinir of claim 7 having the differential scanning calorimetric thermogram of Figure 7.

[10] The crystalline Form C of cefdinir of claim 7 having the characteristic differential scanning calorimetric melting exotherm at about 120-130°C.

[11] The crystalline Form C of cefdinir of claim 7 having the infrared spectrum of Figure 8.

[12] A process for the preparation of crystalline cefdinir, the process comprising:

(a) converting cefdinir or a base addition salt thereof to cefdinir acid addition salt with an acid at a temperature of about 10°C or less;

(b) basifying the acid addition salt of cefdinir with a base; and

(c) isolating crystalline cefdinir.

[13] The process of claim 12, wherein the acid comprises an inorganic or organic acid.

[14] The process of claim 13, wherein the acid comprises one or more of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, trifluoroacetic acid, p-

toluenesulphonic acid, maleic acid, acetic acid and succinic acid.

[15] The process of claim 12, wherein the base comprises an inorganic or organic base.

[16] The process of claim 15, wherein the base comprises one or more of an alkali and alkaline earth metal hydroxide or alkoxide, ammonia, triethylamine, dicyclohexylamine, diisopropylamine, or mixtures thereof.

[17] The process of claim 12, further comprising isolating the acid addition salt of cefdinir.

[18] The process of claim 12, wherein the crystalline cefdinir is the hydrated form of cefdinir.

[19] The process of claim 12, wherein the crystalline cefdinir is either or both of Form B or Form C of cefdinir.

[20] A process for the preparation of crystalline cefdinir, the process comprising:

(a) acidifying a base addition salt of cefdinir at a temperature of 10°C or less; and

(b) isolating the crystalline cefdinir.

[21] The process of claim 20, wherein the acid comprises one or more of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, trifluoroacetic acid, p-toluenesulphonic acid, maleic acid, acetic acid and succinic acid.

[22] A process for the preparation of crystalline Form B or Form C of cefdinir, the process comprising:

(a) dissolving cefdinir or salt thereof in water at pH of about 5.5 to 8;

(b) optionally adding an organic solvent in the solution of step a);

(c) adjusting the pH of the solution obtained in step a) or b) to between 1.0 and 3.0 with an acid; and

(d) isolating crystalline Form B of cefdinir from the reaction mixture obtained thereof.

[23] The process according to claim 22, wherein the organic solvent is added in step b).

[24] The process according to claim 23, wherein the organic solvent used in step b) is water miscible to get Form B.

[25] The process according to claim 24, wherein the organic solvent used in step b) comprises one or more of methanol, ethanol, isopropanol, n-propanol, acetone, acetonitrile, tetrahydrofuran, 1,4-dioxane or mixtures thereof.

[26] The process according to claim 22, wherein the organic solvent used in step b) comprises one or more of alkanols, esters, ketones, acetonitrile, chlorinated hydrocarbons, tetrahydrofuran, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, 1,4-dioxane and dimethylsulphoxide or mixtures thereof to

get Form C.

[27] A pharmaceutical composition comprising a therapeutically effective amount of one or both of the crystalline Form B and the crystalline Form C of cefdinir, and one or more pharmaceutically acceptable carriers, excipients or diluents.

[28] The pharmaceutical composition according to claim 27, wherein the cefdinir comprises either substantially pure crystalline Form B cefdinir or substantially pure crystalline Form C cefdinir.

[29] A method of treating bacterial infections in a warm-blooded animal, the method comprising providing a pharmaceutical composition to the warm-blooded animal, the pharmaceutical composition comprising one or both of the crystalline Form B and the crystalline Form C of cefdinir.

[30] The method according to claim 29, wherein the cefdinir comprises either substantially pure crystalline Form B cefdinir or substantially pure crystalline Form C cefdinir.

FIGURE 1

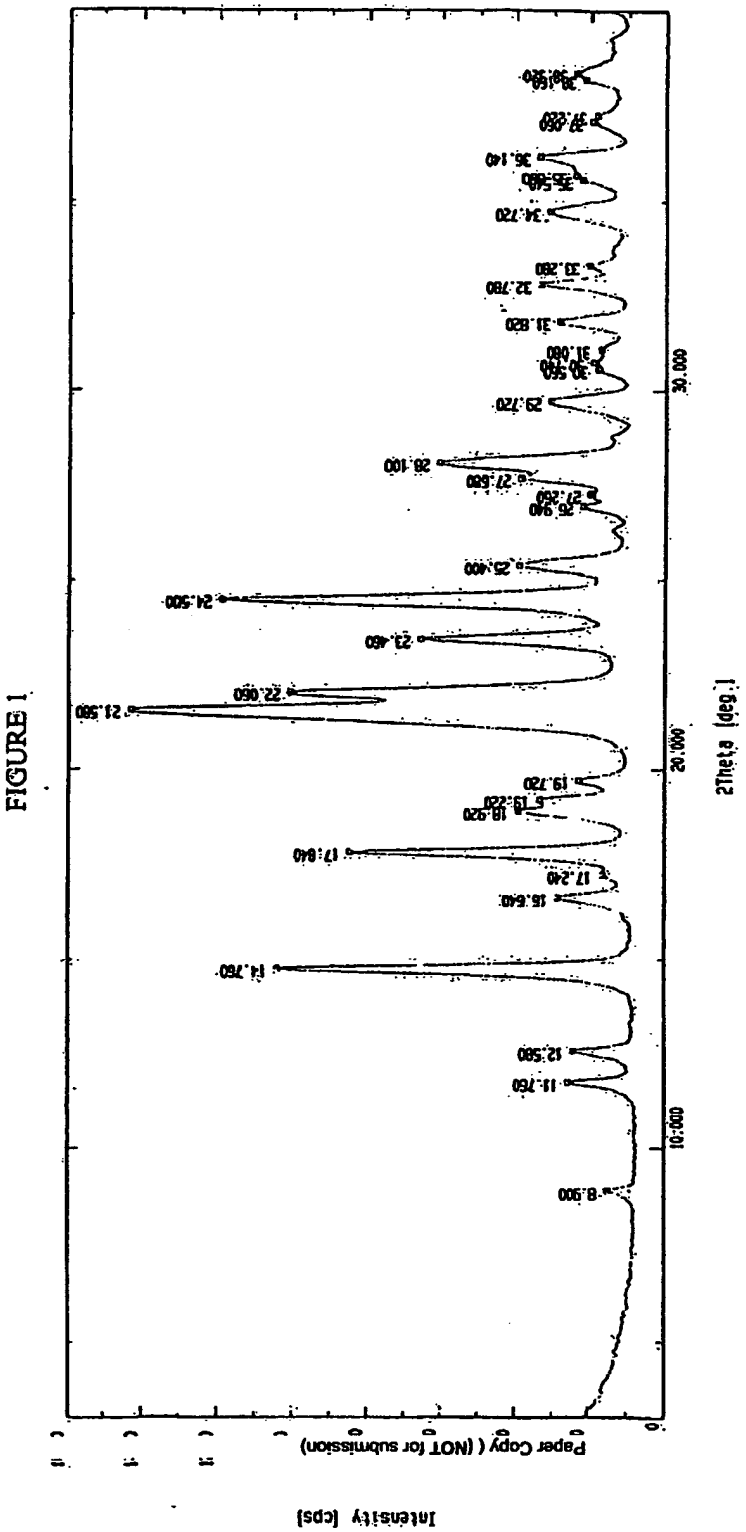

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FIGURE 2.

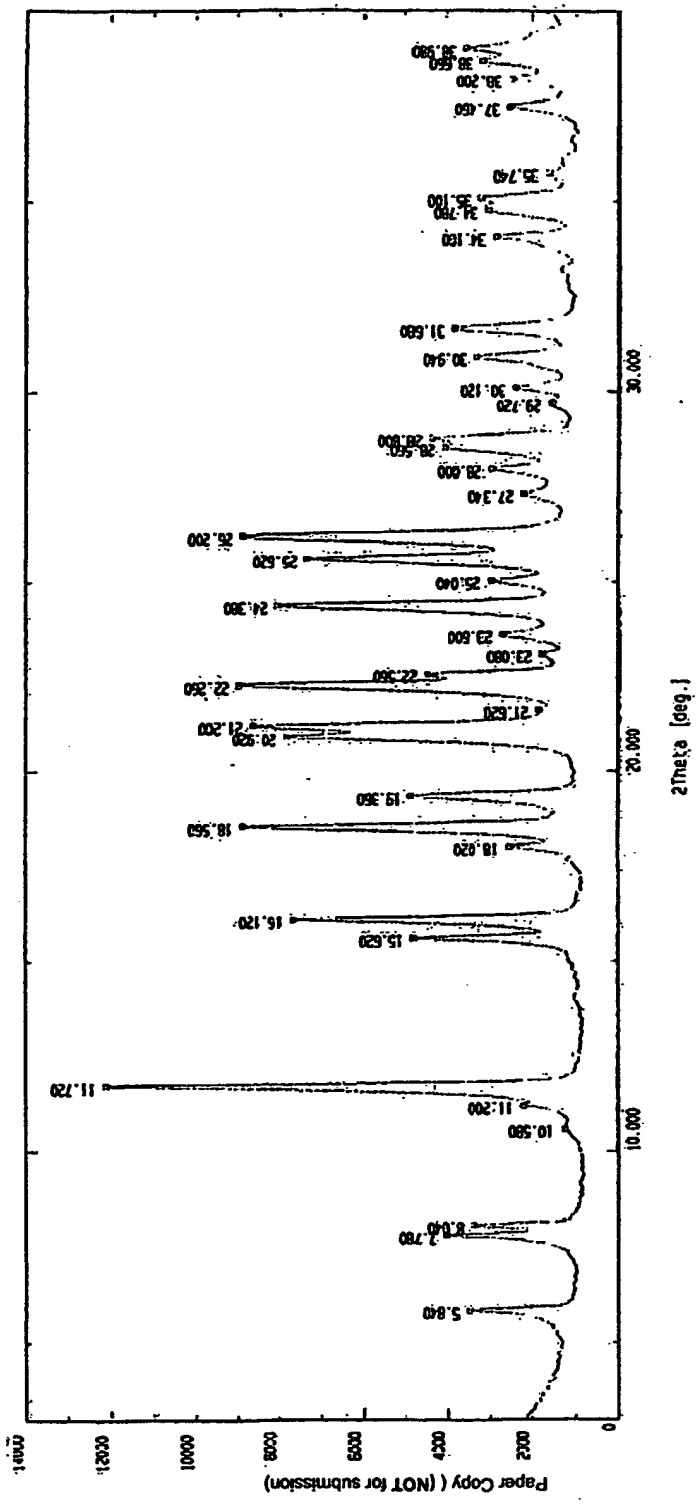
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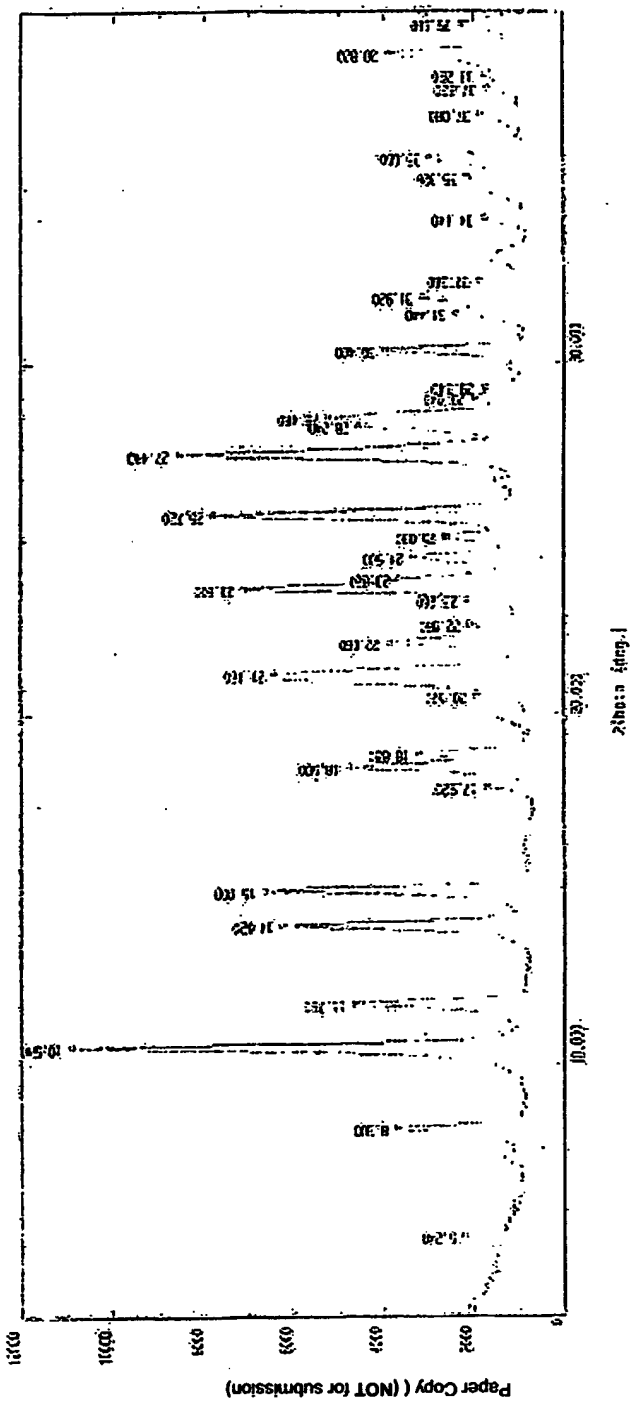
FIGURE 3



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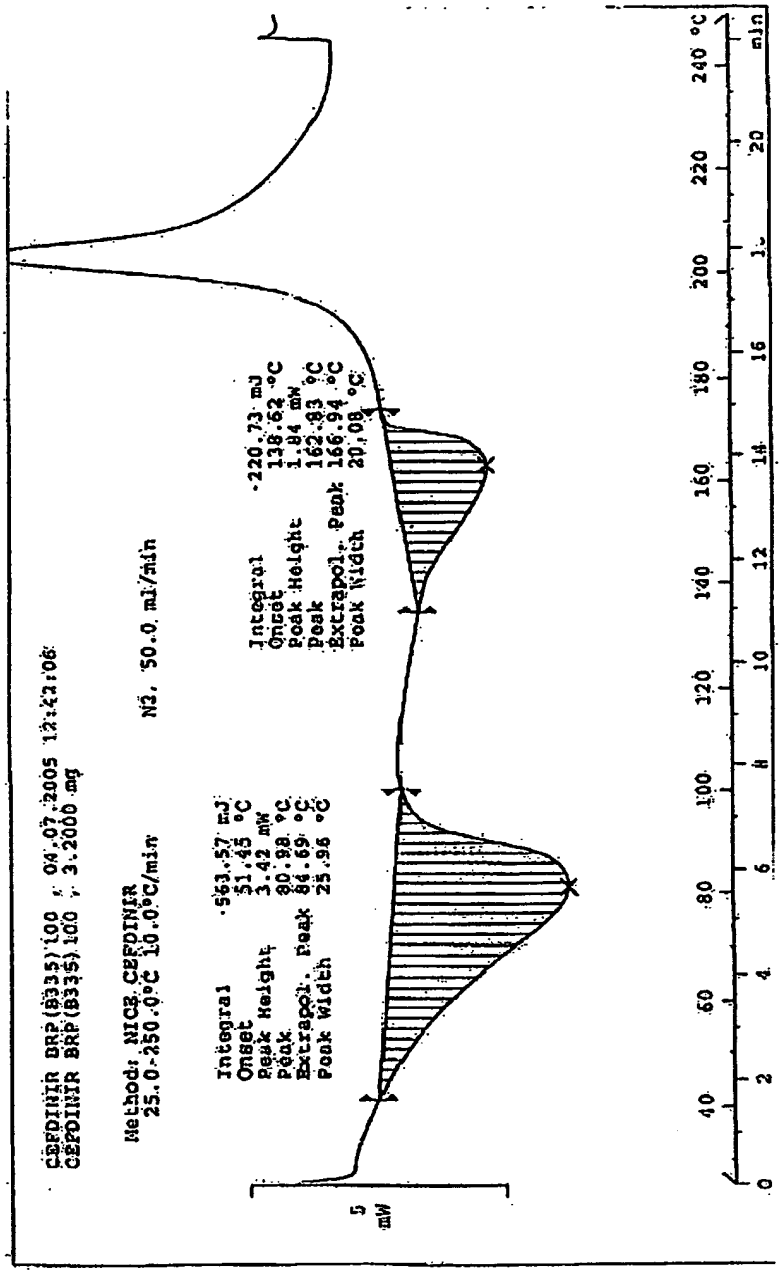

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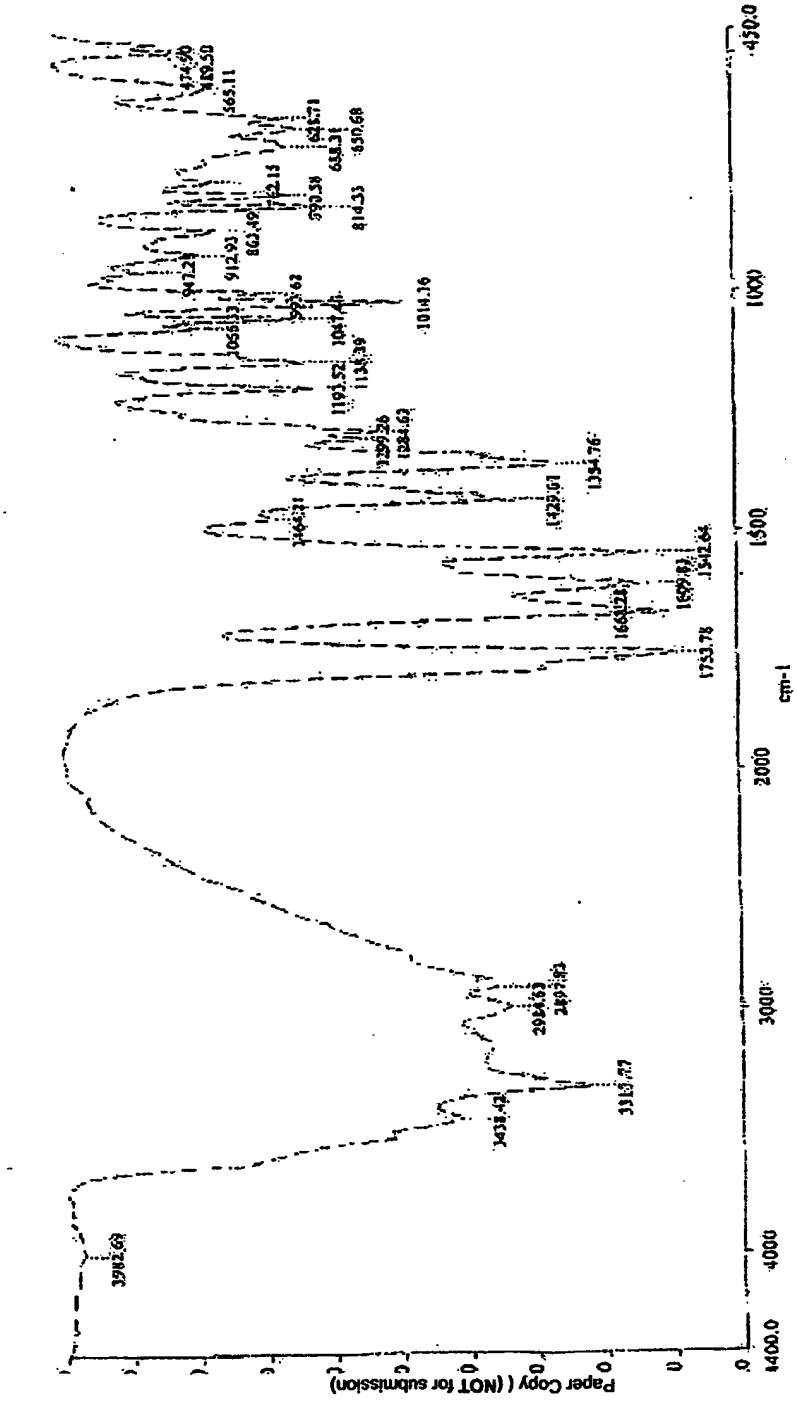
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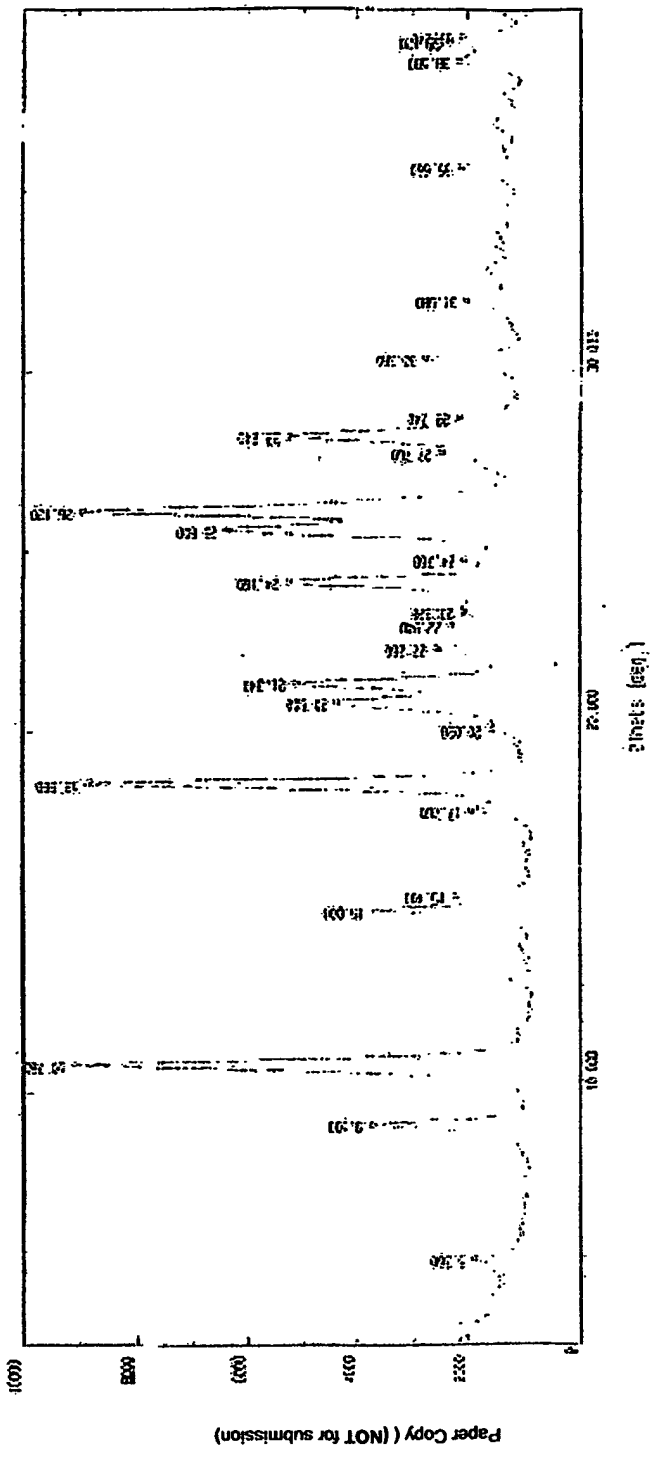

FIGURE 7

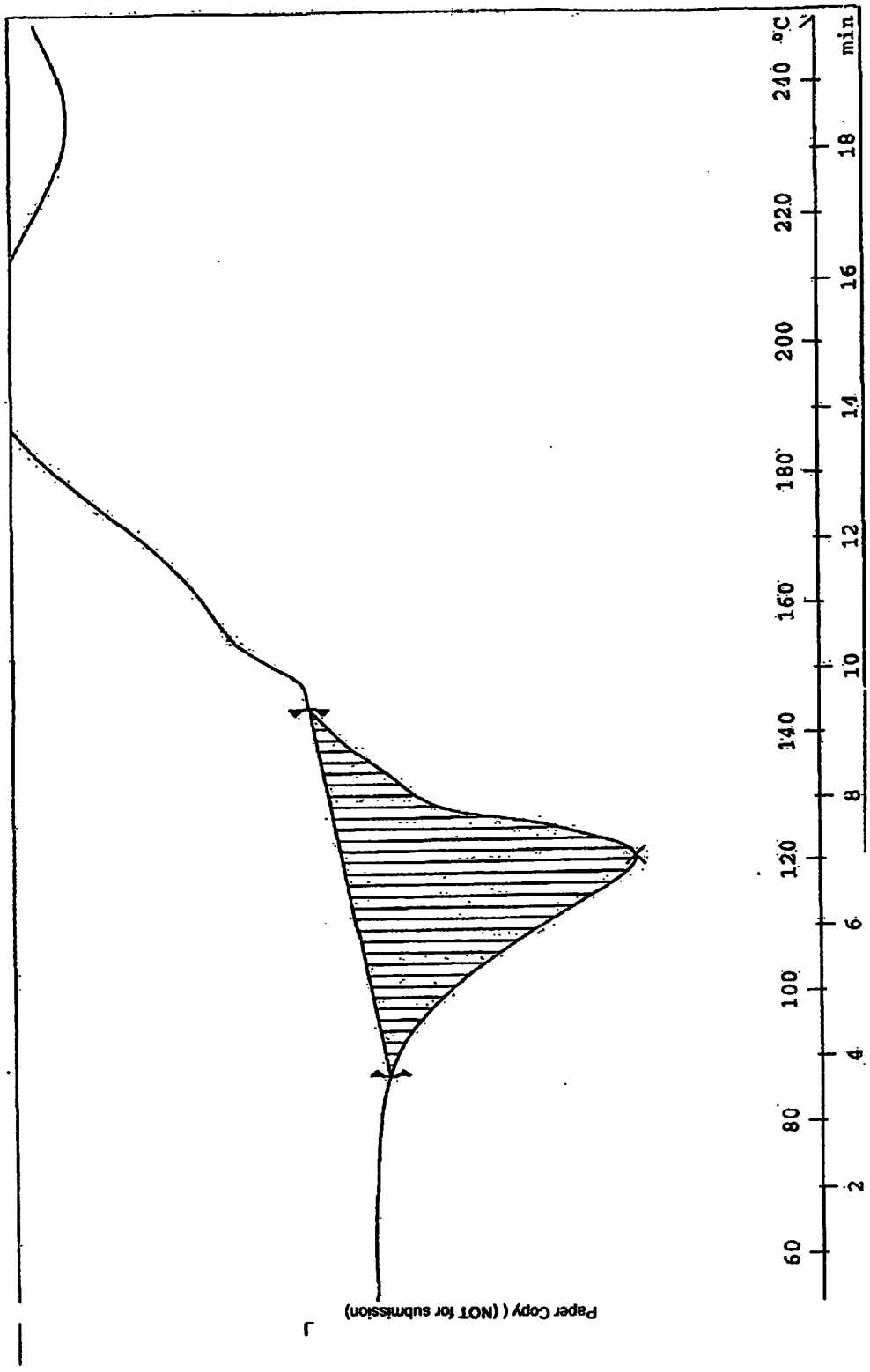
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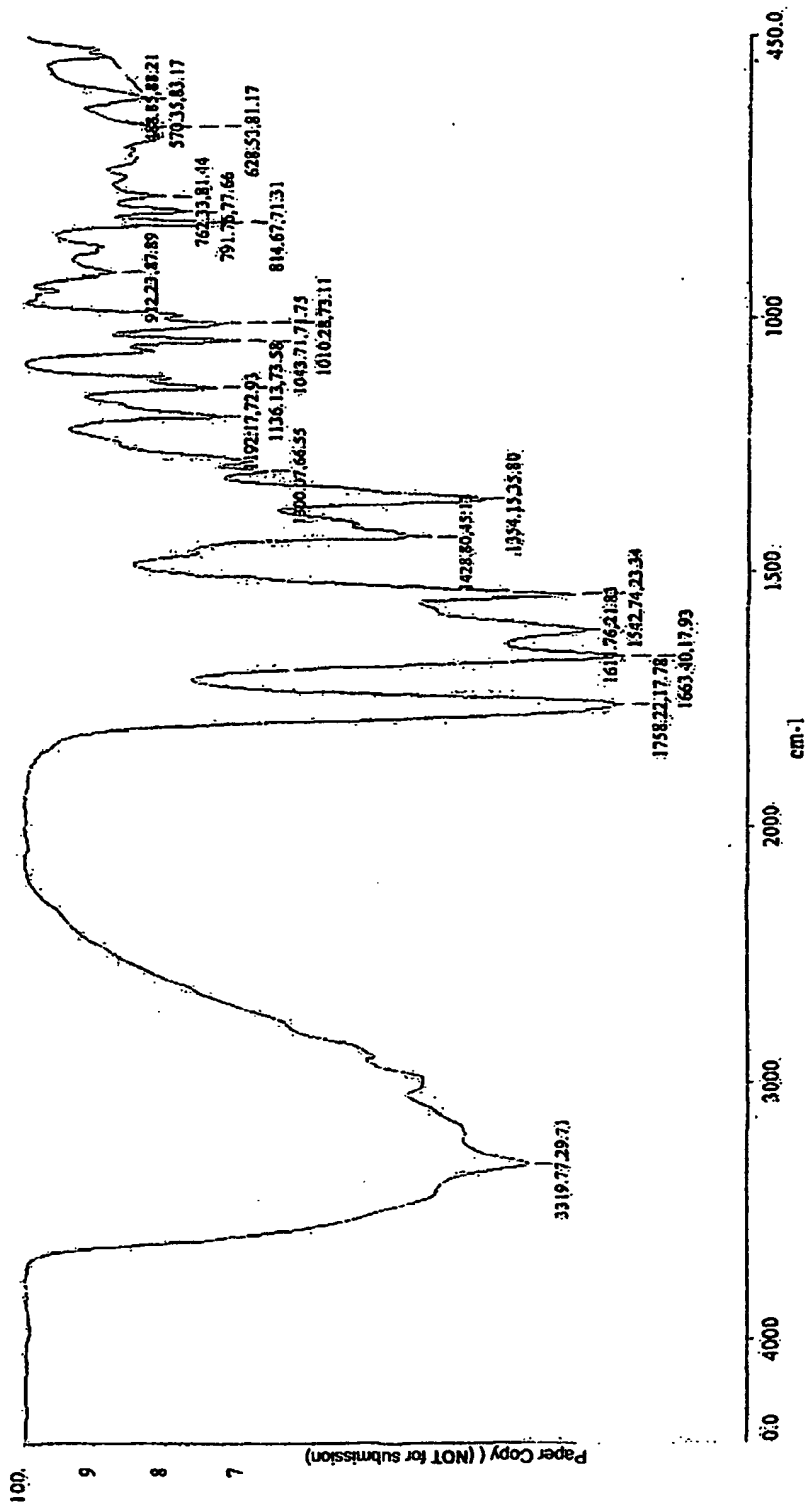
FIGURE 8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